IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

APPEAL BRIEF **PURSUANT TO** **37 C.F.R. §41.37** Address to: Mail Stop Appeal Brief - Patents Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450	Attorney Docket No.	STAN-390
	Confirmation No.	4130
	First Named Inventor	HARBURY, PEHR B.
	Application Number	09/421,422
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	Group Art Unit	1639
	Examiner Name	Liu, Sue Xu
	Title:	"DNA-TEMPLATED COMBINATORIAL LIBRARY CHEMISTRY"

Sir:

Applicant hereby appeals from the Final Rejection dated February 7, 2008 and the Advisory Action dated April 21, 2008. This Appeal Brief is submitted pursuant to the Notice of Appeal dated April 29, 2008 for the above-identified patent application, and thus timely filed.

The brief contains these items under the following headings, and in the order set forth below:

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I. REAL PARTY IN INTEREST

The real party in interest in this matter is The Board of Trustees of the Leleand Stanford Junior University, having an address at1705 El Camino Real, Palo Alto, California 94306-1106.

II. RELATED APPEALS AND INTERFERENCES

There are no other known appeals or interferences which will directly affect or be directly affected by or have bearing on the Board's decision in the pending appeal.

III. STATUS OF CLAIMS

Claims 1, 3-10, and 15-30 are pending and stand rejected in the Final Office Action dated February 7, 2008, and in the Advisory Action dated April 21, 2008. Claims 2 and 11-14 are cancelled. Claims 1, 3-10, and 15-30 are the subject of this Appeal. The pending claims on Appeal are provided in the attached Claims Appendix.

IV. STATUS OF AMENDMENTS

Claims 1, 5, 9, 23 and 29 were amended after final rejection in the Response to Final Office Action dated February 7, 2008. These amendments after final rejection were entered by the Examiner in the Advisory Action dated April 21, 2008. Thus, all claim amendments have been entered by the Examiner.

V. SUMMARY OF CLAIMED SUBJECT MATTER

Although the follow summary and specification citations are given in accordance with C.F.R. § 1.192(c), these citations are merely examples of where support may be found in the specification for this section of the Brief. There is no intention to suggest in any way that the claims are limited to these examples.

A. General Context of Embodiments of the Appellant's Invention

Appellant has developed methods for iterative synthesis and screening of a plurality of compounds in which a nucleic acid tag directs and encodes the synthesis of the compound to which it is covalently attached, and the tag is a DNA molecule which can be amplified biochemically (Specification page 4, lines 15-18). As illustrated in Figure 1 of the drawings, and in the specification beginning on page 6, line 29, the synthesis method is carried out by splitting a pool of the tags into subsets by

hybridization to a complementary sequence, coupling a different chemical subunit to each subset, pooling the subsets, and repeating as necessary until synthesis of the plurality of compounds is complete. Each nucleic acid tag in the pool comprises variable hybridization sequences that are different for each subset of tags (e.g., a_1-j_1, a_2-j_2, a_3-j_3, and a_4-j_4), and a chemical reaction site for coupling the chemical subunit (*Id.*, and specification page 12, line 28 – page 13, line 8). The nucleic acid tags may also include constant spacer sequences (e.g., z_1-z_5) that separate the variable sequences from each other (*Id.*). The variable sequences have orthogonal hybridization properties to facilitate splitting of the pool of tags into subsets by hybridization of each subset to a different complementary sequence (e.g., a_1^c-j_1^c etc. which are complementary to a_1-j_1 etc.) (*Id.*). Thus the above pool of nucleic acid tags, when employed in iterative rounds of splitting by hybridization, coupling, and pooling as noted above, actually directs and encodes the synthesis of a compound to which it is covalently attached, and not merely reporting on the synthetic history of individual compounds as do the prior art methods (*Id.*, and specification page 19, lines 5-13). The importance of these and other factors in the context of the claims on appeal is further set forth below.

B. Independent Claim 1

Independent Claim 1 is directed to a method for synthesizing a plurality of compounds using nucleic acid tags that directs and encodes the synthesis of a compound to which it is covalently attached (e.g., specification page 4, lines 15-18). The method comprises steps (a)-(f), which is illustrated in Figure 1 of the drawings, and in the specification beginning on page 6, line 29 as noted above, and explained further as follows. Step (a) involves providing a pool of subsets of nucleic acid tags in which each tag in the pool comprises a single stranded DNA sequence having a 5' terminus and a first variable hybridization sequence linked to a second variable hybridization sequence (e.g., specification page 4, lines 22-24, page 6, lines 29–32, page 9, lines 14-18, page 12, lines 1-2, and page 12, line 21 – page 13, line 21). The 5' terminus is covalently attached to a chemical reaction site (e.g., specification page 9, lines 10-13, page 13, line 25-page 14, line 4), and each of the first and second variable hybridization sequences is different for each subset of nucleic acid tags (e.g., specification page 4, lines 22-24, page 6, line 31-32, page 9, lines 14-18, page 12, line 21 – page 13, line 21). Step (b) involves splitting the pool of nucleic acid tags of step (a) to form a first group of subsets of nucleic acid tags for participating in a first synthetic reaction, which is carried out by contacting the nucleic acid tags with a plurality of first immobilized nucleotide sequences (e.g., specification page 4, lines 31-33, page 6, line 32-page 7, line 3,

and page 14, line 6-page 15, line 22). The first immobilized sequences are each designed to capture a subset of the nucleic acid tags by specific hybridization between one of the first variable hybridization sequences and one of the first immobilized sequences (e.g., specification page 4, lines 31-33, page 6, line 32-page 7, line 2, and page 7, lines 25-31). The subsets are physically separated on the basis of the first variable hybridization sequence of each nucleic acid tag, and the first immobilized sequence removed (e.g., specification page 15, lines 7-8, and page 16, lines 1-6). Step (c) involves carrying out the first synthetic reaction by reacting the chemical reaction sites of the nucleic acid tags in each of the subsets formed in step (b) with a selected one of a plurality of first reagents that couples a different chemical subunit to the chemical reaction site of each subset of nucleic acid tags (e.g., specification page 4, line 33-page 5, line 5, page 7, lines 3-4, and page 15, line 24-page 16, line 23). The reaction is carried out under conditions effective to form a reagent-specific compound intermediate to produce a first group of subsets of reacted nucleic acid tags (e.g., specification page 4, line 33-page 5, line 1, and page 15, line 24-page 16, line 23). Step (d) involves pooling the first group of subsets of reacted nucleic acid tags of step (c) to form a first pool of reacted nucleic acid tags (e.g., specification page 5, lines 2-5, page 7, lines 4-5, page 14, line 6-page 15, line 22). Step (e) involves splitting the first pool of reacted nucleic acid tags of step (d) to form a second group of subsets of reacted nucleic acid tags for participation in a second synthetic reaction, and is carried out by contacting the first pool of reacted nucleic acid tags with a plurality of second immobilized nucleotide sequences (e.g., specification page 5, lines 2-5, page 7, lines 4-5, and page 14, line 6-page 15, line 22). The second immobilized nucleotide sequences are each designed to capture a subset of the first pool of reacted nucleic acid tags by specific hybridization between one of the second variable hybridization sequences and the second immobilized sequence (e.g., specification page 5, lines 2-5, page 7, lines 4-5, page 7, lines 25-31, and page 14, line 6-page 15, line 22). The subsets of the first pool of reacted nucleic acid tags are then physically separated on the basis of the second variable hybridization sequence of each nucleic acid tag, and the second immobilized sequence removed (e.g., specification page 15, lines 7-8, and page 16, lines 1-6). Step (f) involves carrying out the second synthetic reaction by reacting the reagent-specific compound intermediate of the reacted nucleic acid tag in each of the subsets formed in step (e) with a selected one of a plurality of second reagents that couples a different chemical subunit to the reagent-specific compound intermediate of each subset of reacted nucleic acid tags formed in step (e) (e.g., specification page 5, lines 1-5, page 7, lines 3-5, and page 15, line 24-page 16, line 23). The reaction of step (f) is carried out under conditions effective to form a different sequence oligomer or different sequence small-molecule

compound attached to a nucleic acid tag to produce a second group of subsets of reacted nucleic acid tags (e.g., specification page 5, lines 2-5, page 7, lines 19-24, page 9, lines 4-9, and page 15, line 24-page 16, line 23).

C. Independent Claim 23

Independent Claim 23 is directed to a method for the iterative synthesis and screening of a plurality of compounds to produce a subpopulation of compounds having a desired activity, wherein a nucleic acid tag directs and encodes the synthesis of the compound to which it is covalently attached (e.g., specification page 4, lines 15-18). The method comprises steps (a)-(m), which is illustrated in Figure 1 of the drawings, and in the specification beginning on page 6, line 29 as noted above, and explained further as follows. Step (a) involves providing a pool of subsets of the nucleic acid tags in which each tag in the pool comprises a single stranded DNA sequence having a 5' terminus and a first variable hybridization sequence linked to a second variable hybridization sequence (e.g., specification page 4, lines 22-24, page 6, lines 29–32, page 9, lines 14-18, page 12, lines 1-2, and page 12, line 21 – page 13, line 21). The 5' terminus is covalently attached to a chemical reaction site (e.g., specification page 9, lines 10-13, page 13, line 25-page 14, line 4), and each of the first and second variable hybridization sequences is different for each subset of nucleic acid tags (e.g., specification page 4, lines 22-24, page 6, line 31-32, page 9, lines 14-18, page 12, line 21 – page 13, line 21). Step (b) involves splitting the pool of nucleic acid tags of step (a) to form a first group of subsets of nucleic acid tags for participating in a first synthetic reaction, which is carried out by contacting the nucleic acid tags with a plurality of first immobilized nucleotide sequences (e.g., specification page 4, lines 31-33, page 6, line 32-page 7, line 3, and page 14, line 6-page 15, line 22). The first immobilized nucleotide sequences are each designed to capture a subset of the nucleic acid tags by specific hybridization between one of the first variable hybridization sequences and one of the first immobilized sequences (e.g., specification page 4, lines 31-33, page 6, line 32-page 7, line 2, and page 7, lines 25-31). The subsets are physically separated on the basis of the first variable hybridization sequence of each nucleic acid tag, and the first immobilized sequence removed (e.g., specification page 15, lines 7-8, and page 16, lines 1-6). Step (c) involves carrying out the first synthetic reaction by reacting the chemical reaction sites of the nucleic acid tags in each of the subsets formed in step (b) with a selected one of a plurality of first reagents that couples a different chemical subunit to the chemical reaction site of each subset of nucleic acid tags (e.g., specification page 4, line 33-page 5, line 5, page 7, lines 3-4, and page 15, line 24-page 16, line

23). The reaction is carried out under conditions effective to form a reagent-specific compound intermediate to produce a first group of subsets of reacted nucleic acid tags (e.g., specification page 4, line 33-page 5, line 1, and page 15, line 24-page 16, line 23). Step (d) involves pooling the first group of subsets of reacted nucleic acid tags of step (c) to form a first pool of reacted nucleic acid tags (e.g., specification page 5, lines 2-5, page 7, lines 4-5, page 14, line 6-page 15, line 22). Step (e) involves splitting the first pool of reacted nucleic acid tags of step (d) to form a second group of subsets of reacted nucleic acid tags for participation in a second synthetic reaction, and is carried out by contacting the first pool of reacted nucleic acid tags with a plurality of second immobilized nucleotide sequences (e.g., specification page 5, lines 2-5, page 7, lines 4-5, and page 14, line 6-page 15, line 22). The second immobilized nucleotide sequences are each designed to capture a subset of the first pool of reacted nucleic acid tags by specific hybridization between one of the second variable hybridization sequences and the second immobilized sequence (e.g., specification page 5, lines 2-5, page 7, lines 4-5, page 7, lines 25-31, and page 14, line 6-page 15, line 22). The subsets of the first pool of reacted nucleic acid tags are then physically separated on the basis of the second variable hybridization sequence of each nucleic acid tag, and the second immobilized sequence removed (e.g., specification page 15, lines 7-8, and page 16, lines 1-6). Step (f) involves carrying out the second synthetic reaction by reacting the reagent-specific compound intermediate of the reacted nucleic acid tag in each of the subsets formed in step (e) with a selected one of a plurality of second reagents that couples a different chemical subunit to the reagent-specific compound intermediate of each subset of reacted nucleic acid tags formed in step (e) (e.g., specification page 5, lines 1-5, page 7, lines 3-5, and page 15, line 24-page 16, line 23). The reaction of step (f) is carried out under conditions effective to form a different sequence oligomer or different sequence small-molecule compound to produce a second group of subsets of reacted nucleic acid tags (e.g., specification page 5, lines 2-5, page 7, lines 19-24, page 9, lines 4-9, and page 15, line 24-page 16, line 23). Step (g) involves subjecting the second group of subsets of reacted nucleic acid tags produced in step (f) to one or more additional rounds of (i) pooling to form an Nth pool of reacted nucleic acid tags, (ii) splitting to form and Nth group of subsets of reacted nucleic acid tags, and (iii) synthesis to produce subsets of Nth reacted nucleic acid tags, where each round includes an additional step-specific subset of Nth variable hybridization sequences and Nth immobilized nucleotide sequences (e.g., specification page 5, lines 2-5, page 7, lines 4-5, and page 12, lines 9-13). Step (g) comprises steps (h)-(m). Step (h) involves forming an Nth pool of reacted nucleic acid tags, wherein each of said nucleic acid tags of step (a) comprises the Nth variable hybridization sequence linked to the second variable

hybridization sequence, wherein each of the first, second and Nth variable hybridization sequences is different for each subset of nucleic acid tags (e.g., specification page 5, lines 2-5, page 7, lines 4-5, page 14, line 6-page 15, line 22). Step (i) involves splitting the Nth pool of reacted nucleic acid tags of step (h) to form an Nth group of subsets of reacted nucleic acid tags for participating in an Nth reaction step, by contacting said Nth pool of reacted nucleic acid tags with a plurality of said Nth immobilized nucleotide sequences (e.g., specification page 5, lines 2-5, page 7, lines 4-5, and page 14, line 6-page 15, line 22). The Nth immobilized sequences are each designed to capture a subset of the reacted nucleic acid tags by specific hybridization between one of said Nth variable hybridization sequences and the Nth immobilized sequence (e.g., specification page 5, lines 2-5, page 7, lines 4-5, page 7, lines 25-31, and page 14, line 6-page 15, line 22). The subsets of the Nth pool are then physically separated on the basis of the Nth variable hybridization sequence of each reacted nucleic acid tag, and the Nth immobilized sequence removed (e.g., specification page 15, lines 7-8, and page 16, lines 1-6). Step (j) involves carrying out the Nth reaction step by reacting the reacted nucleic acid tags in each of the subsets formed in step (i) with a selected one of a plurality of Nth-reaction reagents that couples a different chemical subunit to the different sequence oligomer or different sequence small-molecule compound of each subset formed in step (i) (e.g., specification page 5, lines 2-5, page 7, lines 4-5, page 7, lines 19-24, page 9, lines 4-9, and page 15, line 24-page 16, line 23). The reaction of Step (j) is carried out under conditions effective to produce subsets of Nth reacted nucleic acid tags (e.g., specification page 5, lines 2-5, and page 15, line 24-page 16, line 23). Step (k) involves repeating steps (h) - (j) if necessary, until synthesis of a plurality of compounds is complete (e.g., specification page 5, lines 2-5). Step (l) involves identifying from said plurality of compounds of step (k), one or more compounds having a desired activity to yield a subpopulation of nucleic acid tags (e.g., specification page 5, lines 19-20, and page 6, lines 8-11). Step (m) involves producing a pool of nucleic acid tags based on the subpopulation of nucleic acid tags from step (l) and repeating steps (a) – (l) if necessary, until synthesis of a plurality of compounds having the desired activity is complete (e.g., specification page 5, line 19-page 6, line 7).

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

Are Claims 1, 3-10, and 15-30 properly rejected under 35 U.S.C. § 103(a) as being unpatentable over Lerner et al. (US 5,573,905) ("Lerner") in view of Brenner et al. (US 5,635,400) ("Brenner")?

VII. ARGUMENT

The rejection of Claims 1, 3-10 and 15-30 under 35 U.S.C. §103(a) over Lerner in view of Brenner is not sustainable.

Claims 1, 3-10 and 15-30

The Examiner states that Lerner teaches a method for synthesizing combinatorial chemical libraries using nucleic acid tags. The Examiner concedes that Lerner lacks any specific teaching of hybridization-based splitting for compound synthesis. For this, the Examiner looks to Brenner, which the Examiner asserts as teaching a method of "sorting" nucleic acid tags by hybridization.

The Examiner argues that it would have been obvious to one of ordinary skill in the art at the time of the invention to modify Lerner's method of compound library synthesis in view of Brenner's hybridization-based sorting method to arrive at Appellant's claimed invention. The Examiner specifically cites the Abstract, column 12, lines "10+" and "15+",[1] Figure 4 and columns 19-20 of Brenner for disclosing use of oligonucleotide tags for hybridization-based "sorting" in general.

However, the only examples cited by the Examiner in Brenner that remotely relate to compound synthesis (column 12, lines "10+" and "15+", Figure 4) are for identifying specific compounds in a library *once it has already been made and screened for hits*. In other words, in the context of a method for compound synthesis, Brenner teaches the use of hybridization for sorting oligonucleotide tagged compounds after synthesis of the compound library is already completed. In fact, Brenner states as much (See Brenner column 12, in reference to Figure 4, beginning at line 10 where it states "After synthesis is completed …" selection (230) followed by sorting (240) are carried out (emphasis added)). In no instance does Brenner teach or suggest the use of hybridization-based splitting to facilitate the steps of synthesis of a plurality of compounds, much less the specific method claimed by Appellant. No where does Lerner remedy the deficiency of Brenner.

With respect to general knowledge of one of ordinary skill in the art and the motivation to combine the references as argued by the Examiner (i.e., in the absence of any specific disclosure or teaching in either reference to do so), Appellant notes that Dr. Sydney Brenner is a named inventor on both the Lerner and later filed Brenner patents currently cited against Appellant's claims. Despite this apparent link between these references, the combined references fail to point toward the claimed

[1] Appellants note that references such as "10+" indicate the line numbers as noted in the Office Action.

invention. In fact, Dr. Brenner specifically teaches in his later filed patent (Brenner) that when a compound synthesis method according to his earlier filed patent (Lerner) is used, that any hybridization-based sorting is carried out after compound synthesis and selection is already completed (Brenner column 11, lines 25-column 12, line 3 for compound synthesis method, and Brenner column 12, lines 10 and 15, for hybridization-based sorting after synthesis and selection is completed). The Examiner has erred in ignoring the specific teaching of Brenner in order to satisfy the shortcomings of both Lerner and Brenner, rendering the rejection untenable. Appellant respectfully submits that the Examiner's rational of combining the references in the rejection based on some general alleged motivation at the time of the invention is erroneous and can only be made in hindsight using Appellant's disclosure and claimed invention as a guide.

Accordingly, whether taken singly, or in combination with Lerner, Brenner cannot comprise a colorable basis for a rejection of Appellant's claimed invention as set forth in Claims 1, 3-10, and 15-30 and the Examiner should be reversed.

In addition, Appellant submits that it would not have been obvious to one of ordinary skill in the art, at the time of the invention, to modify Lerner's method of compound synthesis in view of Brenner's hybridization-based sorting of oligonucleotides to arrive at Appellant's claimed invention, because neither reference alone or together teaches or suggests any compound synthesis method that employs a nucleic acid tag that "directs and encodes" the synthesis of a compound to which it is covalently attached.

As claimed, Appellant's methods employ nucleic acid tags having a chemical reaction site "wherein each nucleic acid tag comprises a single stranded DNA sequence having a 5' terminus and a first variable hybridization sequence linked to a second variable hybridization sequence, wherein said 5' terminus is covalently attached to a chemical reaction site, and wherein each of said first and second variable hybridization sequences is different for each subset of nucleic acid tags." These different variable hybridization sequences are exploited in the method to split a pool of nucleic acid tags into subsets, and subject the subsets to chemical reactions with different chemical subunits. Thus, the variable hybridization sequences can be said to "direct" and "encode" the synthesis of the compound attached to each corresponding nucleic acid tag. Because the variable hybridization sequences necessary for directing and encoding compound synthesis in Appellant's claimed method are preexisting in the nucleic acid tags before any of the required splitting and compound synthesis steps ever takes place, each nucleic acid tag (1) fully encodes the synthesis of a compound before any synthesis is carried out,

and (2) directs the synthesis of a compound to which it is attached (when employed as claimed in the methods) by routing the fully encoded tag (by hybridization-based splitting) to a particular subset for a selected coupling reaction that corresponds to that subset, and thus is pre-defined by a given combination of different variable hybridization sequences in the tag.

In contrast, Lerner's method begins with a bifunctional linker devoid of any nucleic acid sequences that are exploited, for sequential, alternate step-wise addition of a chemical subunit and its corresponding nucleic acid "code" in a compound synthesis process (see, e.g., Lerner Figure 2, and column 9, line 56 – column 11, line 60, and Example 9). Thus, in contrast to the nucleic acid tag employed in Appellant's claimed method, Lerner teaches a tag that is built sequentially during and in conjunction with his compound synthesis method by step-wise chain assembly to report on the corresponding step-wise synthetic history of a compound. Lerner's support or tags at any synthesis stage cannot be used to both direct and encode synthesis, because the nucleic acid material that reports on the presence of a given chemical subunit is missing from the tag (and thus fails to provide a hybridization target) until added in conjunction with the corresponding chemical subunit. As noted in Appellant's specification, "The principle advantage of the current invention over previous methods for constructing and screening combinatorial compound libraries is that the tag directs and encodes the synthesis of the compound to which it is covalently attached (not merely reporting on the synthetic history of individual compounds) …" among others (Specification page 19, lines 6-9). Brenner fails to remedy the deficiency in Lerner, because Brenner discloses essentially the same sequential compound synthesis method as Lerner (See Brenner column 11, line 65 – column 12, line 3). Furthermore, Brenner only teaches or suggests application of the oligonucleotide tags for "sorting" by hybridization after compound synthesis is completed, as discussed above.

For the reasons stated above, neither Lerner nor Brenner, whether taken singly or in combination with each other, can comprise a colorable basis for the rejection of Appellant's claimed invention as set forth Claims 1, 3-10 and 15-30, and these claims should be passed to issue.

Claims 7, 22, 29 and 30 (Separately patentable)

Claims 7 and 22 further limit the method of independent Claim 1, and Claims 29-30 further limit the method of independent Claim 23. These claims are non-obvious over Lerner in view of Brenner for the reasons stated above. Claims 7, 22, 29 and 30 are separately patentable and further distinguished from the cited combination of references. Neither reference taken singly or together teach or suggest a

method of Claim 1 or 23 that employs a nucleic acid tag according to any of Claims 7 and 22, or Claims 29 and 30, respectively. Specifically, the methods according to Claims 7, 22, 29 and 30 each require that the tags within each subset comprises, for each subset of variable hybridization sequences, an adjacent constant spacer sequence separating that variable hybridization sequence from an adjacent one, each of the constant spacer sequences being the same for all subsets and each variable hybridization sequence being different for each subset.

The Examiner asserts that Lerner teaches sequences within a library of tags share common nucleic acid sequence while possessing constant and variable sequences, which "read on" Claims 7 and 29, and cites the sequences of Figure 2 of Lerner in support of the rejection. The Examiner also asserts that Lerner at column 4, lines "35+" teaches making chemical polymers with various lengths, and at column 6, lines "1+" teaches "the length of a unit identifier oligonucleotide can vary depending on the complexity of the library..." The Examiner concludes that although the reference does not explicitly teach the oligonucleotides are at least 50 nucleotides long as recited in Claims 22 and 30, it would have been *prima facie* obvious for one of ordinary skill in the art to use oligonucleotides with various sizes (such as the ones that are at least 50 nucleotides long) and that, depending on the experimental design and the desired polymers to be synthesized (such as the needed increase in complexity of the library), would have been motivated to use oligonucleotides with appropriate lengths to generate a combinatorial library.

The Examiner's conclusion is erroneous, and thus the Examiner's combination of Lerner in view of Brenner untenable. In addition to the linker and synthesized compounds, Figure 2 of Lerner, which depicts aspects of Lerner's synthesis method, contains two basic types of nucleic acid sequences: (i) the individual nucleotide reporter sequences used to report on the synthetic history of a tagged compound, which sequences are the same for each subset regardless of location or position in a tag (e.g., each "gly" or glycine at any and every position in all compounds of Figure 2 corresponds to the same CACATG nucleotide reporter sequence), and (ii) terminal PCR primer sequences that do not separate any nucleic acid sequences. That Lerner at column 4, lines "35+" may disclose making chemical polymers with various lengths, and at column 6, lines "1+" that "the length of a unit identifier oligonucleotide can vary depending on the complexity of the library..." does not change this basic fact.

This is in contrast to a method according to any of Claims 7, 22, 29 or 30 that employs nucleic acid tags in which the tags within each subset comprises for each subset of variable hybridization sequences: (i) an adjacent constant spacer sequence separating that variable hybridization sequence from

an adjacent one, each of the constant spacer sequences being the same for all subsets, and (ii) each variable hybridization sequence being different for each subset. No where does Brenner remedy this insufficiency of Lerner, neither reference suggests such tag features, and as noted above, Brenner's sorting by hybridization of tags after compound synthesis is already completed adds nothing. Thus, Lerner and Brenner taken alone or together fail to teach or suggest a method of Claim 7, 22, 29 or 30.

In addition, Appellant submits that application of Brenner's sorting by hybridization to Lerner's sequential synthesis method cannot direct and encode the synthesis of a plurality of compounds in accordance with any of Appellant's method Claims 7, 22, 29 and 30. It is readily apparent that Lerner's method would be frustrated by any sorting by hybridization according to the Examiner's application of Brenner, because as illustrated in the method of Figure 2 of Lerner, there is nothing in Lerner's tags to hybridize to until after the nucleic acid sequence is added (e.g., CACATG) in conjunction with the corresponding chemical subunit (e.g., gly). This is in contrast to Appellant's method in that all of the variable hybridization sequences of the recited nucleic acid tags that direct and encode the synthesis of a compound to which it is attached are already present in the tag before any compound synthesis ever takes place.

Moreover, in contrast to Appellant's method that employs tags in which each variable hybridization sequence is different for each subset, Lerner teaches a method that employs tags with chemical subunit "codes" that are the same for each subset of tags regardless of location or position in a tag. Thus, Lerner's tags cannot direct and encode the synthesis of a plurality of compounds in accordance with Appellant's claimed method. Lerner's tags at best only reflect the order in which the nucleic acid sequence was already added in the context of all prior-added nucleotide sequences, i.e., to define both what the chemical subunit is and where that subunit is positioned in the compound. This is one reason why Lerner's method requires sequential "coding" in order for it to work (See Lerner Figure 2, and column 5, line 59-column 6, line 1). Thus, Lerner's "codes" can only be used to report on the synthetic history of a tagged compound. As noted above, nothing in Lerner or Brenner alone or together teaches or suggest why one of ordinary skill in the art would have been motivated to discard Lerner's tags, re-design them so that each variable hybridization sequence is different for each subset, ignore Lerner's sequential coding method of compound synthesis, and then somehow modify Lerner's teachings to employ "sorting" by Brenner to arrive at Appellant's claimed invention. Appellant respectfully submits that such a re-construction project can only be carried out in hindsight using Appellant's disclosure and claimed invention as a guide.

The compound synthesis method of Lerner taken singly or in view of Brenner's sorting by hybridization results in a method that only reports on the synthetic history of a compound. that Neither reference taken singly or together teaches or suggests a method for the synthesis of a plurality of compounds according to Claims 7, 22, 29 and 30. Accordingly, the rejection of these claims should be reversed.

Claims 8-9 (Separately patentable)

Claims 8-9 further limit the method of Claim 1, and are non-obvious over Lerner in view of Brenner for the reasons stated above. Claim 8 and its dependent Claim 9 are separately patentable and further distinguished from the cited combination of references in that neither reference teaches a method of Claim 1 as limited by Claims 8 or 9 that requires the additional steps of: identifying from the plurality of compounds produced by the method of Claim 1, one or more compounds having a desired activity to yield a subpopulation of nucleic acid tags, and using the subpopulation to carry out the method of Claim 1.

The Examiner states that Lerner at column "15+" and at text bridging columns 17-18 teaches enriching compound libraries using the PCR / restriction products for bifunctional molecules that bind to biologically active molecules, which "read on" the enriching steps of Claim 8 or the intended uses of Claims 8 and 9. The Examiner's characterization of Lerner is misguided, and thus the Examiner's combination with Brenner erroneous. Lerner at column "15+" teaches attaching the oligonucleotide tagged compounds to a surface after synthesis is already completed. Lerner at text bridging column 17-18 teaches use of PCR to make hybridization probes for screening after synthesis is already completed. Thus the sections of Lerner relied on by the Examiner for support of the rejection do not involve any method of tag-directed compound synthesis. In no instance are the hybridization probes or the nucleic acid portions of Lerner's tagged compounds ever used (or suggested for use) to produce a subpopulation of nucleic acid tags that are then deployed in a method of compound synthesis according to Claim 1 as required by Appellant's Claims 8 and 9. Likewise, nothing in Brenner teaches or suggests using any tagged compounds to produce a subpopulation of nucleic acid tags that are then deployed in a method of compound synthesis according to Claim 1 as required by method Claims 8 and 9. Thus, Brenner fails to remedy the deficiency of Lerner, rendering the Examiner's combination of Lerner and Brenner erroneous. In fact, as with Lerner and noted above, Brenner teaches sorting by hybridization after compound synthesis has already occurred, and does not teach using any subpopulation of tags for

compound synthesis. Appellant submits that the motivation to ignore these teachings is completely missing. As such, Lerner's sequential compound synthesis method taken with Brenner's oligonucleotide sorting by hybridization in no way teaches or suggests the methods according to Claims 8 and 9, and the rejection should be reversed.

Claim 10 (Separately patentable)

Claim 10 depends from Claim 7, which depends from Claim 1, and is non-obvious over Lerner in view of Brenner for the reasons stated above. Claim 10 is separately patentable over the cited references for the reasons stated above for Claim 7, and those that follow. Method Claim 10 requires that each of the constant spacer sequences comprises a unique restriction enzyme site, and that the method further comprises the steps of: (g) identifying from the plurality of compounds, one or more compounds having a desired activity to yield a subpopulation of nucleic acid tags; (h) amplifying the subpopulation of nucleic acid tags by polymerase chain reaction (PCR); (i) treating the subpopulation of nucleic acid tags with one or more restriction enzymes under conditions effective to produce a partial digest; (j) rejoining the partially digested nucleic acid tags; and (k) adding a new chemical reaction site to said partially digested nucleic acid tags and using the subpopulation to carry out the method of Claim 1.

The Examiner states that Lerner "reads on" Claim 10 where it teaches the steps of "PCR amplification, subsequent restriction digestion of the PCR product, rejoining the digested strands, etc." The Examiner cites Lerner Figure 1, column 3, lines "60+", column 7, and column 17, lines "45+" in support of this part of the rejection. The Examiner also states that Lerner "reads on" Claim 10 where it teaches enriching the libraries using the PCR / restriction products for bifunctional molecules that bind to biologically active molecules, and cites Lerner columns 17-18, bridging in support of this aspect of the rejection.

Here again the Examiner's characterization of the Lerner reference is misguided, and thus the Examiner's combination of the references flawed. First, Lerner at the cited sections (Lerner Figure 1, column 3, lines "60+", column 7, and column 17-18 bridging) teaches amplification by PCR of the entire oligonucleotide tag sequence after synthesis of a tagged compound is completed (Lerner column 2, lines 61 – 67). Lerner indicates that such PCR products can be used for cloning and sequencing (Lerner column 7, lines 13-17), and as hybridization probes (Lerner columns 17, lines 55-58). As noted

above, Brenner teaches or suggest the same as Lerner, namely, PCR amplification of the tags after compound synthesis is already completed.

Second, no where does Lerner teach a method that requires treating a subpopulation of PCR-amplified nucleic acid tags with one or more restriction enzymes in which the subpopulation possesses the features required by Claim 10. For instance, Lerner does not teach or suggest any PCR-amplified oligonucleotide tags with constant spacer sequences that separate each variable hybridization sequence, much less such PCR-amplified tags in which each of the constant spacer sequences comprises a unique restriction enzyme site as required by Claim 10. Nor does Lerner teach partial digestion of such tags as required by the method of Claim 10. For example, Figure 1 of Lerner teaches full restriction digestion to generate the entire "coding sequence" of the oligonucleotide tag. This is consistent with Lerner's stated purposes of use of the PCR products in cloning and sequencing and use as hybridization probes as noted above. In fact, even if one assumes that Lerner teaches that each of the individual "code" sequences making up the "coding sequence" of his PCR-amplified tags are each separated by unique restriction sites, which it does not, treatment of such hypothetical tags by restriction digestion would render the enriching purpose of Lerner's method useless. The information content of the oligonucleotide tag library would be destroyed through its disassembly into to non-distinguishable fragments containing a mixture of redundant sequences that each code for individual chemical subunits and nothing more.

Moreover, nowhere does Lerner teach (j) rejoining partially digested nucleic acid tags; and (k) adding a new chemical reaction site to the partially digested nucleic acid tags and using the subpopulation to carry out the method of Claim 1. It is simply not there. And again, nothing in Brenner teaches or suggests modifying the method of Lerner to remedy this deficiency. For example, following the Examiner's logic of applying Brenner's sorting by hybridization method to Lerner's, one ends with using, for example, a fully digested mixture containing fragments with the same sequences from both the same and other oligonucleotide tags for hybridization. The Examiner is then left to explain how such fragments (which are now de-enriched by their reduction into nothing more than codes for individual chemical subunits) can be used to enrich for anything, much less deploy those fragments to carry out the method of Claim 1.

For the reasons stated above, neither Lerner nor Brenner, whether taken singly or in combination with each other, can comprise a colorable basis for the rejection of Appellant's claimed invention as set forth in Claim 10, and this claim should be passed to issue.

Claim 16 (Separately patentable)

Claim 16 depends from Claim 1, and is non-obvious over Lerner in view of Brenner for the reasons stated above. Claim 16 is separately patentable and further distinguished from the cited combination of references in that neither reference teaches a method of Claim 1 that further requires transferring of the subsets from the immobilized sequence to a solid support prior to carrying out the synthetic reacting steps (c) and (f).

The Examiner states that Lerner at column 18 teaches attaching the oligonucleotide onto a solid support and then conducting further oligonucleotide synthesis, which "reads on" the solid support attachment of Claim 16. This is simply not true. Lerner at column 18 teaches PCR amplification for sequencing of the oligonucleotide tagged compounds after synthesis is already complete. Nowhere in column 18 is there reference to transferring anything to any solid support, much less in the context of compound synthesis that involves transferring of nucleic acid tag subsets from an immobilized sequence to a solid support prior to carrying out the synthetic reacting steps of Claim 1 as required by Claim 16.

Appellant notes that in the context of synthesis on a solid support, Lerner teaches that the oligonucleotide tag and corresponding compound are attached to the same linker, which in turn is attached to the solid support. The tag, compound, and linker remain attached throughout synthesis (Lerner column 8, lines 14-53, and column 27 Example 8). Lerner further teaches that the tagged compound is released from the support by cleavage after synthesis is completed (Lerner column 8, lines 43-45, and column 27 Example 8). In fact, in no instance does Lerner's synthesis method involve transfer of any nucleic acid tags from an immobilized sequence to a solid support prior to carrying out any synthetic reacting step for Lerner's coupling a chemical subunit in his compound synthesis method.

Brenner fails to remedy the deficiency of Lerner, rendering the Examiner's combination of the references defective. Brenner's sorting by hybridization is carried out after synthesis is already completed as noted above, and in no case does Brenner teach or suggest transfer of any nucleic acid tags from an immobilized sequence to a solid support prior to carrying out any reacting step for coupling a chemical subunit in a compound synthesis method. As such, Lerner's sequential compound synthesis method taken with Brenner's oligonucleotide sorting by hybridization in no way teaches or suggests the method according to Claim 16, and the rejection should be reversed.

Advisory Action

In the Advisory Action, the Examiner stated that Appellant appeared to variously attack the Lerner and Brenner references alone, as opposed to the combination applied by the Examiner. Appellant respectfully disagrees. Appellant endeavored to address the untenable nature of the Examiner's combination in the context of Appellant's understanding of the rejection, and earnestly respond to individual mischaracterizations of the references made by the Examiner to expose underlying flaws in the combination's premise. In light of the Advisory Action, Appellant has reiterated and clarified these arguments above with respect to the final rejection on Appeal.

Appellant addresses specific new points raised in the Advisory Action below.

The Examiner stated that the specification does not provide an explicit and specific definition for oligonucleotides that can "encode" and that Appellant's reference to "pre-coded" tags is not a limitation of the claims. First, the specification explains that the nucleic acid tags of Appellant's invention direct and encode the synthesis of a compound to which it is covalently attached (e.g., specification page 4, lines 15-17), that the tag encodes the hybridization-based splitting steps (e.g., specification page 14, lines 12-13, and page 15, lines 1 and 6), and thus the encoded combinatorial chemical libraries produced in accordance with Appellant's synthesis methods (e.g., specification page 10, line 32-page 11, line 2). Second, Appellant used the 'pre-coded' analogy to simply aid the Examiner in understanding the claimed invention versus the prior art. As noted above, the nucleic acid tags of Appellant's invention physically embody this feature as disclosed and claimed, as all nucleic acid tags employed in Appellant's methods contain all the variable hybridization sequences necessary to direct and encode the synthesis of a compound to which it is covalently attached before compound synthesis is carried out.

The Examiner also stated that the definition of "variable hybridization sequence" is broad and encompasses any nucleic acid sequence. This is simply not true. The portion of the specification cited by the Examiner refers to "the hybridization sequences" of an exemplary embodiment (specification page 12, lines 30-32) which, in the context of that embodiment and the nucleic acid tags of the invention, are described throughout the as-filed specification as sequences with orthogonal hybridization properties (e.g., specification page 6, lines 31-32). This feature is illustrated in the specification in the context of a degenerate pool of nucleic acid tags representing 111 different variable or "V" hybridization sequences that "are orthogonal to each other with respect to hybridization, meaning that none of the 111 sequences cross-hybridizes efficiently with another of the 111 sequences, or with the complement to any

of the other 111 sequences, at the temperature Tm" (e.g., specification page 12, line 25-page 13, line 21).

For reasons of record and as summarized above, Lerner and Brenner taken singly or together cannot comprise a colorable basis for a rejection of Appellant's claimed invention as set forth in Claims 1, 3-10 and 15-30, and these claims should be passed to issue.

VIII. CLAIMS APPENDIX

A copy of each of the claims involved in this appeal, namely Claims 1, 3-10 and 15-30, is attached as a Claims Appendix.

IX. EVIDENCE APPENDIX

None.

X. RELATED PROCEEDINGS

None.

XI. CONCLUSION

For the foregoing reasons, Appellant respectfully requests that the Board direct the Examiner in charge of this case to withdraw the rejection of Claims 1, 3-10 and 15-30 under § 103(a) over Lerner in view of Brenner.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number STAN-390.

Respectfully submitted,
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CLAIMS APPENDIX

1. (**Previously presented**) A method of tag-directed synthesis of a plurality of compounds wherein a nucleic acid tag directs and encodes the synthesis of a compound to which it is covalently attached, comprising:

(a) providing a pool of subsets of nucleic acid tags, wherein each nucleic acid tag comprises a single stranded DNA sequence having a 5' terminus and a first variable hybridization sequence linked to a second variable hybridization sequence, wherein said 5' terminus is covalently attached to a chemical reaction site, and wherein each of said first and second variable hybridization sequences is different for each subset of nucleic acid tags;

(b) splitting the pool of nucleic acid tags of step (a) to form a first group of subsets of nucleic acid tags for participating in a first synthetic reaction, by contacting said nucleic acid tags with a plurality of first immobilized nucleotide sequences, each designed to capture a subset of said nucleic acid tags by specific hybridization between one of said first variable hybridization sequences and one of said first immobilized sequences, and physically separating the subsets of said pool of nucleic acid tags on the basis of said first variable hybridization sequence of each nucleic acid tag and removing said first immobilized sequence;

(c) carrying out the first synthetic reaction by reacting the chemical reaction sites of the nucleic acid tags in each of the subsets formed in step (b) with a selected one of a plurality of first reagents that couples a different chemical subunit to the chemical reaction site of each subset of nucleic acid tags under conditions effective to form a reagent-specific compound intermediate to produce a first group of subsets of reacted nucleic acid tags;

(d) pooling the first group of subsets of reacted nucleic acid tags of step (c) to form a first pool of reacted nucleic acid tags;

(e) splitting the first pool of reacted nucleic acid tags of step (d) to form a second group of subsets of reacted nucleic acid tags for participation in a second synthetic reaction, by contacting said first pool of reacted nucleic acid tags with a plurality of second immobilized nucleotide sequences, each designed to capture a subset of said first pool of reacted nucleic acid tags by specific hybridization between one of said second variable hybridization sequences and the second immobilized sequence, and physically separating the subsets of said first pool of reacted nucleic acid tags on the basis of said second

variable hybridization sequence of each nucleic acid tag and removing said second immobilized sequence; and

(f) carrying out the second synthetic reaction by reacting the reagent-specific compound intermediate of the reacted nucleic acid tag in each of the subsets formed in step (e) with a selected one of a plurality of second reagents that couples a different chemical subunit to the reagent-specific compound intermediate of each subset of reacted nucleic acid tags formed in step (e) under conditions effective to form a different sequence oligomer or different sequence small-molecule compound attached to a nucleic acid tag to produce a second group of subsets of reacted nucleic acid tags, whereby a plurality of compounds is produced.

2. (**Cancelled**)

3. (**Previously presented**) The method of claim 1, wherein the plurality of first and second reagents in steps (c) and (f) include different oligomer subunits.

4. (**Previously presented**) The method of claim 1, wherein the plurality of first and second reagents in steps (c) and (f) include different small molecule compound substituents.

5. (**Previously presented**) The method of claim 1 for making a plurality of compounds requiring more than 2 synthetic steps wherein the second group of subsets of reacted nucleic acid tags produced in step (f) is subjected to one or more additional rounds of (*i*) pooling to form an Nth pool of reacted nucleic acid tags, (*ii*) splitting to form an Nth group of subsets of reacted nucleic acid tags, and (*iii*) synthesis to produce subsets of Nth reacted nucleic acid tags, and wherein each round includes an additional step-specific subset of Nth variable hybridization sequences and Nth immobilized nucleotide sequences for each synthetic step N greater than 2 and which further comprises, for each additional synthetic step N;

(g) forming an Nth pool of reacted nucleic acid tags, wherein each of said nucleic acid tags of step (a) comprises said Nth variable hybridization sequence linked to said second variable hybridization sequence, and wherein each of said first, second and Nth variable hybridization sequences is different for each subset of nucleic acid tags;

(h) splitting the Nth pool of reacted nucleic acid tags of step (g) to form an Nth group of subsets of reacted nucleic acid tags for participating in an Nth reaction step, by contacting said Nth pool of reacted nucleic acid tags with a plurality of said Nth immobilized nucleotide sequences, each designed to capture a subset of said reacted nucleic acid tags by specific hybridization between one of said Nth variable hybridization sequences and the Nth immobilized sequence, and physically separating the subsets of said Nth pool on the basis of said Nth variable hybridization sequence of each reacted nucleic acid tag and removing said Nth immobilized sequence;

(i) carrying out the Nth reaction step by reacting the reacted nucleic acid tags in each of the subsets formed in step (h) with a selected one of a plurality of Nth-reaction reagents that couples a different chemical subunit to the different sequence oligomer or different sequence small-molecule compound of each subset formed in step (h) under conditions effective to produce subsets of Nth reacted nucleic acid tags; and

(j) repeating steps (g) - (i) if necessary, until synthesis of the compounds is complete.

6. (**Previously presented**) The method of claim 5 wherein each subset of nucleic acid tags includes at least 5 separate variable hybridization sequences.

7. (**Previously presented**) The method of claim 1, wherein said nucleic acid tags within each subset further comprises for each subset of variable hybridization sequences, an adjacent constant spacer sequence separating that variable hybridization sequence from an adjacent one, each of said constant spacer sequences being the same for all subsets of nucleic acid tags and each variable hybridization sequence being different for each group of subsets of nucleic acid tags.

8. (**Previously presented**) The method according to claim 1, for use in enriching the plurality of compounds for those having a desired compound activity, further comprising identifying from said plurality of compounds, one or more compounds having a desired activity to yield a subpopulation of nucleic acid tags, and using the subpopulation to carry out the method of claim 1.

9. (**Previously presented**) The method according to claim 8, wherein said using the subpopulation includes:

amplifying said subpopulation of nucleic acid tags by polymerase chain reaction (PCR), and

adding a chemical reaction site.

10. (**Previously presented**) The method of claim 7, wherein each of said constant spacer sequences comprises a unique restriction enzyme site, and wherein the method further comprises:

(g) identifying from said plurality of compounds, one or more compounds having a desired activity to yield a subpopulation of nucleic acid tags;

(h) amplifying said subpopulation of nucleic acid tags by polymerase chain reaction (PCR);

(i) treating said subpopulation of nucleic acid tags with one or more restriction enzymes under conditions effective to produce a partial digest;

(j) rejoining said partially digested nucleic acid tags; and

(k) adding a new chemical reaction site to said partially digested nucleic acid tags and using the subpopulation to carry out the method of claim 1.

11.-14. (**Canceled**)

15. (**Previously presented**) The method of claim 1, wherein each of said first and second immobilized nucleotide sequences are each bound to the surface of a solid phase reagent.

16. (**Previously presented**) The method of claim 1, wherein said steps (c) and (f) include first transferring the subsets of said nucleic acid tags from said immobilized sequences to a solid support prior to said reacting.

17. (**Previously presented**) The method of claim 1, wherein said chemical reaction site is covalently attached to said 5' terminus through a linker.

18. (**Previously presented**) The method of claim 1, wherein said chemical reaction site is a chemical component capable of forming a chemical bond selected from amide, ester, urea, urethane, carbon-carbonyl bonds, carbon-nitrogen bonds, carbon-carbon single bonds, olefin bonds, thioether bonds, and disulfide.

19. (**Previously presented**) The method of claim 1, wherein said chemical subunits are amino acids.

20. (**Previously presented**) The method of claim 19, wherein said chemical reaction site is a primary amine, said amino acids are Fmoc-protected amino acids, said reacting couples a selected Fmoc-protected amino acid to said primary amine to form an amide bond, and said reacting is followed by removal of the Fmoc protecting group of said selected Fmoc-amino acid prior to a next reacting step.

21. (**Previously presented**) The method of claim 20, wherein said reagent-specific compound intermediate is an amino acid presenting a new primary amine ready for a next reacting step.

22. (**Previously presented**) The method of claim 7, wherein said variable hybridization sequences and said constant spacer sequences are catenated nucleotide sequences each at least 10 nucleotides long, and wherein said nucleic acid tag includes at least 5 variable hybridization sequences.

23. (**Previously presented**) A method for the iterative synthesis and screening of a plurality of compounds to produce a subpopulation of compounds having a desired activity, wherein a nucleic acid tag directs and encodes the synthesis of the compound to which it is covalently attached, said method comprising:

(a) providing a pool of subsets of the nucleic acid tags in which each nucleic acid tag comprises a single stranded DNA sequence having a 5' terminus and a first variable hybridization sequence linked to a second variable hybridization sequence, wherein said 5' terminus is covalently attached to a chemical reaction site, and wherein each of said first and second variable hybridization sequences is different for each subset of nucleic acid tags;

(b) splitting the pool of nucleic acid tags of step (a) to form a first group of subsets of nucleic acid tags for participating in a first synthetic reaction, by contacting said nucleic acid tags with a plurality of first immobilized nucleotide sequences, each designed to capture a subset of said nucleic acid tags by specific hybridization between one of said first variable hybridization sequences and one of said first immobilized sequences, and physically separating the subsets of said pool of nucleic acid tags

on the basis of said first variable hybridization sequence of each nucleic acid tag and removing said first immobilized hybridization sequence;

(c) carrying out the first synthetic reaction by reacting the chemical reaction sites of the nucleic acid tags in each of the subsets formed in step (b) with a selected one of a plurality of first reagents that couples a different chemical subunit to the chemical reaction site of each subset of nucleic acid tags under conditions effective to form a reagent-specific compound intermediate to produce a first group of subsets of reacted nucleic acid tags;

(d) pooling the first group of subsets of reacted nucleic acid tags of step (c) to form a first pool of reacted nucleic acid tags;

(e) splitting the pool of the first group of reacted nucleic acid tags of step (d) to form a second group of subsets of reacted nucleic acid tags for participation in a second synthetic reaction, by contacting said first pool of reacted nucleic acid tags with a plurality of second immobilized nucleotide sequences, each designed to capture a subset of said first pool of reacted nucleic acid tags by specific hybridization between one of said second variable hybridization sequences and the second immobilized sequence, and physically separating the subsets of said first pool on the basis of said second variable hybridization sequence of each nucleic acid tag and removing said second immobilized sequence;

(f) carrying out the second synthetic reaction by reacting the reagent-specific compound intermediate of the reacted nucleic acid tag in each of the subsets formed in step (e) with a selected one of a plurality of second reagents that couples a different chemical subunit to the reagent-specific compound intermediate of each subset of reacted nucleic acid tags formed in step (e) under conditions effective to form a different sequence oligomer or different sequence small-molecule compound to produce a second group of subsets of reacted nucleic acid tags;

(g) subjecting the second group of subsets of reacted nucleic acid tags produced in step (f) to one or more additional rounds of (*i*) pooling to form an Nth pool of reacted nucleic acid tags, (*ii*) splitting to form and Nth group of subsets of reacted nucleic acid tags, and (*iii*) synthesis to produce subsets of Nth reacted nucleic acid tags, wherein each round includes an additional step-specific subset of Nth variable hybridization sequences and Nth immobilized nucleotide sequences, and wherein each additional round comprises:

(h) forming an Nth pool of reacted nucleic acid tags, wherein each of said nucleic acid tags of step (a) comprises said Nth variable hybridization sequence linked to said second variable

hybridization sequence, wherein each of said first, second and Nth variable hybridization sequences is different for each subset of nucleic acid tags;

(i) splitting the Nth pool of reacted nucleic acid tags of step (h) to form an Nth group of subsets of reacted nucleic acid tags for participating in an Nth reaction step, by contacting said Nth pool of reacted nucleic acid tags with a plurality of said Nth immobilized nucleotide sequences, each designed to capture a subset of said reacted nucleic acid tags by specific hybridization between one of said Nth variable hybridization sequences and the Nth immobilized sequence, and physically separating the subsets of said Nth pool on the basis of said Nth variable hybridization sequence of each reacted nucleic acid tag and removing said Nth immobilized sequence;

(j) carrying out the Nth reaction step by reacting the reacted nucleic acid tags in each of the subsets formed in step (i) with a selected one of a plurality of Nth-reaction reagents that couples a different chemical subunit to the different sequence oligomer or different sequence small-molecule compound of each subset formed in step (i) under conditions effective to produce subsets of Nth reacted nucleic acid tags;

(k) repeating steps (h) - (j) if necessary, until synthesis of a plurality of compounds is complete;

(l) identifying from said plurality of compounds of step (k), one or more compounds having a desired activity to yield a subpopulation of nucleic acid tags; and

(m) producing a pool of nucleic acid tags based on the subpopulation of nucleic acid tags from step (l) and repeating steps (a) – (l) if necessary, until synthesis of a plurality of compounds having the desired activity is complete.

24. (**Previously presented**) The method of claim 23, wherein said chemical reaction site is covalently attached to said 5' terminus through a linker.

25. (**Previously presented**) The method of claim 23, wherein said chemical reaction site is a chemical component capable of forming a chemical bond selected from amide, ester, urea, urethane, carbon-carbonyl bonds, carbon-nitrogen bonds, carbon-carbon single bonds, olefin bonds, thioether bonds, and disulfide.

26. (**Previously presented**) The method of claim 23, wherein said chemical subunits are amino acids.

27. (**Previously presented**) The method of claim 26, wherein said chemical reaction site is a primary amine, said amino acids are Fmoc-protected amino acids, said reacting couples a selected Fmoc-protected amino acid to said primary amine to form an amide bond, and said reacting is followed by removal of the Fmoc protecting group of said selected Fmoc-amino acid prior to a next reacting step.

28. (**Previously presented**) The method of claim 27, wherein said reagent-specific compound intermediate is an amino acid presenting a new primary amine ready for a next reacting step.

29. (**Previously presented**) The method of claim 23, wherein said nucleic acid tags within each subset further comprises for each subset of variable hybridization sequences, an adjacent constant spacer sequence separating that variable hybridization sequence from an adjacent one, each of said constant spacer sequences being the same for all subsets of nucleic acid tags and each variable hybridization sequence being different for each group of subsets of nucleic acid tags.

30. (**Previously presented**) The method of claim 29, wherein said variable hybridization sequences and said constant spacer sequences are catenated nucleotide sequences each at least 10 nucleotides long, and wherein said nucleic acid tag includes at least 5 variable hybridization sequences.